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LONG-TERM EFFECTS OF FINASTERIDE ON PROSTATE SPECIFIC ANTIGEN LEVELS: RESULTS FROM THE PROSTATE CANCER PREVENTION TRIAL

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ABSTRACT

Purpose: Studies have shown that finasteride decreases prostate specific antigen (PSA) by approximately 50% during the first 12 months of use. We estimated the long-term effects of finasteride on PSA in men with and without a prostate cancer diagnosis at the end of the study.

Materials and Methods: We analyzed serial PSA in participants in the Prostate Cancer Prevention Trial who had an end of study biopsy (928 with cancer and 8,620 with negative biopsy) or an interim diagnosis of prostate cancer (671). Linear mixed effects regression models were fit to longitudinal PSA values beginning 1 year after randomization.

Results: In subjects with no cancer in the end of study biopsy PSA in the finasteride arm showed a median annual decrease of 5% after year 1, while PSA in the control arm showed an annual increase of 3% ($p < 0.001$). In end of study cases PSA increased annually by 6% (placebo) and 7% (finasteride). In those with interim diagnoses PSA increased by 11% (placebo) and 15% (finasteride) each year prior to diagnosis. Cases with high grade disease (Gleason 7 and above) had greater PSA increases than cases with low grade disease ($p < 0.001$).

Conclusions: In men who have been receiving finasteride for more than 1 year time varying adjustment factors may be needed to determine whether PSA is in the normal range. In the Prostate Cancer Prevention Trial cohort the adjustment factor required to preserve median PSA increased from 2 at 24 months to 2.5 at 7 years after the initiation of finasteride.

KEY WORDS: prostate, prostatic neoplasms, mass screening, finasteride, prostate-specific antigen

In the last decade medical management has supplanted surgical intervention as the primary treatment for symptomatic benign prostatic hyperplasia (BPH).[1,2] The original α-blocking approach, which produced popular agents such as terazosin and doxazosin, was more recently complemented by the addition of hormonally based agents such as finasteride[3] or dutasteride.[4] Finasteride, a 5α-reductase inhibitor, acts chemically by blocking dihydrotestosterone production and shrinking prostate volume.[2,5] Clinical trials have shown that finasteride is safe and efficacious for alleviating BPH symptoms.[3,6,7] Given its safety profile and mechanism of action, the potential of finasteride as a chemopreventive agent for prostate cancer was evaluated by the Prostate Cancer Prevention Trial (PCPT), a joint venture of the National Cancer Institute and Southwest Oncology Group.[8] PCPT enrolled 18,882 men who were randomly assigned to receive placebo or finasteride for 7 years. The trial, which ended in 2003, showed that the prostate cancer prevalence during the 7-year study period decreased by 24.8% in the intervention group but finasteride was associated with an increase in the frequency of apparent high grade disease.[8]

Given the high prevalence of symptomatic BPH[9] and the increase in prostate cancer incidence since the advent of prostate specific antigen (PSA) testing,[10] an enormous number of men are potential candidates for finasteride as a preventive or a therapeutic agent. In 1996 sales of α-blocking agents and finasteride for BPH relief were almost $200 million.[1] It is important to understand how these agents affect PSA concentrations in men without a prostate cancer diagnosis, so that appropriate PSA reference ranges can be developed for screening purposes. The effects of finasteride on PSA have been studied in several cohorts of men with symptomatic BPH.[11–13] Initial results indicated that finasteride causes an average 50% decrease in PSA by 1 year following the initiation of treatment.[11] This 50% decrease also appeared to apply at the individual level, leading to the multiply by 2 rule, which recommends that PSA in men on finasteride should be doubled before being compared with standard reference ranges. Given this information, PCPT initially adopted the multiply by 2 rule for the purpose of interpreting annual PSA measurements in men on the intervention arm of the trial. However, based on the goal of an equal percent of interim biopsies within each study arm the factor was changed to 2.3 in year 4 of the study.[8]

Previous studies of the effects of finasteride on PSA have generally focused on the population of men with symptomatic BPH. PCPT presents us with a unique opportunity to study the impact of finasteride in a large population group, including but not restricted to men with BPH. The size of the trial also enables us to evaluate for the first time whether finasteride acts differently in different racial groups and in cases with different Gleason grades. Finally, the duration of the trial allows us to study the effects of finasteride on PSA during a much longer followup than that in previous studies. Using these data we can explore whether findings previously

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established in the short term in men with symptomatic BPH apply equally well in the long-term to the broader population.

MATERIALS AND METHODS

PCPT was a multicenter, randomized, double-blind study.[8] Between October 1993 and May 1997, 18,882 healthy men 55 years or older were enrolled and randomized to receive 5 mg finasteride daily or placebo. Men who reported a history of prostate cancer or who showed symptoms of BPH were excluded, as were men with abnormal digital rectal examination (DRE) or PSA above 3.0 ng/ml. The goal of including only men with low PSA was to remove as many prevalent prostate cancer cases as possible. Participant evaluation consisted of 2 clinic visits and 2 telephone contacts yearly. At each participant visit treatment side effects were evaluated, compliance was assessed by monitoring pill counts and new pills were dispensed. Once yearly as part of their annual physical examination men were required to undergo DRE and a PSA test. Serum samples were sent to a central laboratory, where PSA was measured and, when applicable, adjusted for finasteride use. Adjustment consisted of multiplying the observed PSA level in the finasteride group by a factor of 2 for the first 3 years of the trial and by 2.3 thereafter. If the DRE result was positive or adjusted PSA was above 4.0 ng/ml, biopsy was recommended. A total of 2,122 men in the finasteride group and 2,348 in the placebo group had biopsy recommended during the course of the trial. Participants not diagnosed with prostate cancer by the end of the study were asked to undergo an end of study biopsy. Approximately 60% of participants had end point information (positive for prostate cancer or a negative end of study biopsy) by the time that the trial was stopped.

To be eligible for the current analysis participants had to have had at least 2 PSA measurements beyond baseline, while continuously on treatment, and an interim diagnosis of prostate cancer or an end of study biopsy, ie disease status at study completion had to be defined. We classified prostate cancer cases as interim cases—diagnosed as a result of a positive screening test or as end of study cases—detected by an end of study biopsy done in the absence of a positive screening test. Participants with a positive PSA test at the end of study year 7 were included with interim cases. Interim cases were further subdivided into 2 groups, that is those in whom cancer was detected following a positive PSA test (PSA detected) and those in whom cancer was detected in the absence of a positive PSA test (nonPSA detected). PSA below the lower limit of detectability (ie 0.3 ng/ml) were set to this value.

A linear mixed effects model[14] was fit to the logarithm of longitudinal PSA values beginning 12 months following randomization. The model allowed for individual specific baseline PSA as well as individual specific PSA velocity, thereby, accounting for the correlation between serial observations in the same individual. Separate models were fit to subjects with negative end of study biopsies (noncases), positive end of study biopsies (end of study cases) and cases diagnosed before the end of study biopsy (interim diagnoses). In prostate cancer cases with more than 4 years of PSA measurements we used data from only the last 4 years to focus on that part of the PSA trajectory that was most relevant to the disease process. In models fit to interim diagnoses the final PSA measurement was omitted because the biopsy recommendation depended on this value. Terms were included after controlling for family history to allow the effect of finasteride on PSA to differ by race (black or other vs white) and to differ by Gleason grade (less than 7 vs 7 or greater) in models fit to cancer cases.

RESULTS

Table 1 shows the characteristics of the study population, which consisted of 928 subjects with disease diagnosed at the end of study biopsy, 671 with interim diagnoses and 8,620 with a negative end of study biopsy. In each group the number of PSA measurements was balanced across the study arms. Of interim diagnoses 435 were detected due to increased PSA and 236 were diagnosed in the absence of a positive PSA test.

Linear mixed effects regression analysis showed PSA growth was significantly associated with disease status and treatment group assignment (table 2). Race and family history of prostate cancer did not show consistent associations with PSA across study groups. Age was significantly associ-

TABLE 1. *Participant characteristics*

	Placebo		Finasteride	
Diagnosed at end of study biopsy:				
No. pts	602		326	
Mean age at randomization (range)	64	(55–80)	64	(55–78)
No. white race (%)	573	(95)	298	(91)
No. black race (%)	17	(3)	20	(6)
No. other races (%)	12	(2)	10	(3)
Median No. measurements (range)	7	(2–11)	7	(2–10)
Mean ng/ml PSA at study yr 1 (range)	1.43	(0.3–12)	0.79	(0.3–5)
% Prostate Ca family history	20		21	
% High grade disease (Gleason score at least 7)	15		27	
Diagnosed at interim biopsy:				
No. pts	392		279	
Mean age at randomization (range)	64	(55–83)	65	(55–82)
No. white race (%)	357	(91)	254	(91)
No. black race (%)	22	(6)	16	(6)
No. other races (%)	13	(3)	9	(3)
Median No. measurements (range)	5	(2–9)	5	(2–9)
Mean ng/ml PSA at study year 1 (range)	2.21	(0.3–15)	1.09	(0.3–4.3)
% Prostate Ca family history	20		24	
% High grade disease (Gleason score at least 7)	34		54	
Neg at end of study biopsy:				
No. pts	4,446		4,174	
Mean age at randomization (range)	63	(55–84)	63	(55–85)
No. white race (%)	4,147	(93)	3,869	(93)
No. black race (%)	135	(3)	134	(3)
No. other races (%)	164	(4)	171	(4)
Median No. measurements (range)	7	(2–16)	7	(2–12)
Mean ng/ml PSA at study year 1 (range)	1.35	(0.3–15)	0.72	(0.2–30)
% Prostate Ca family history	16		15	

Patients who went off treatment were excluded from analysis.

TABLE 2. *Linear mixed effect model results*

Variable	Coefficient	p Value
Diagnosed pos on end of study biopsy (last 4 PSAs in 928 pts):		
Finasteride	−0.916	<0.0001
Time	0.048	<0.0001
High grade (Gleason score at least 7)	−0.059	0.476
Family history	0.026	0.717
Age	0.006	0.065
Black race	0.099	0.047
Other race*	−0.095	0.044
Time × finasteride	0.007	0.450
Time × high grade	0.058	<0.0001
Diagnosed pos on interim biopsy (last 4 PSAs excluding final PSA in 671 pts):		
Finasteride	−0.872	<0.0001
Time	0.079	<0.0001
High grade (Gleason score at least 7)	−0.092	0.132
Family history	−0.001	0.985
Age	−0.006	0.166
Black race	0.045	0.355
Other race*	−0.083	0.060
Time × finasteride	0.019	0.179
Time × high grade	0.086	<0.0001
Neg on end of study biopsy (8,620 pts):		
Finasteride	−0.596	<0.0001
Time	0.031	<0.0001
Family history	0.085	<0.0001
Age	0.007	<0.0001
Black race	0.022	0.255
Other race*	0.002	0.879
Time × finasteride	−0.049	<0.0001

Estimates are from linear regression of log(PSA) on treatment group, time, family history, race and disease status in patients with prostate cancer.

* Hispanic, black Hispanic, Asian or Pacific Islander, or American Indian.

ated with PSA only in subjects with a negative biopsy at the end of the study.

Tables 3 and 4 show the results of our linear regression analyses in terms of the estimated percent change in PSA yearly in select participant subgroups. The figure shows these results graphically.

In placebo group subjects PSA generally increased with time with a median annual increase of 3% in noncases, 6% in end of study cases and 11% in those with interim diagnoses ($p < 0.01$, table 4). The increased growth rate in interim diagnoses appeared to have been driven mostly by PSA detected cases, who had a median annual PSA increase of 12%, in contrast to nonPSA detected cases, who had a median annual PSA increase of only 6% (table 4).

In prostate cancer cases in the placebo group PSA growth was significantly associated with grade, as evidenced by significant time × high grade interaction terms in the models (interim diagnoses and end of study cases $p < 0.001$). Table 4 shows that PSA increased more rapidly in men with high grade disease than in men with low grade disease. Of interim diagnoses on the placebo arm high grade cases had an estimated annual increase of 18%, while low grade cases had an annual increase of 8%. Similarly of cases on the placebo arm detected at the end of study biopsy high grade cases had an estimated annual increase of 11%, while the annual change in low grade cases was only 5%.

TABLE 3. *Estimated annual percent change in PSA in end of study cases and noncases*

Arm	Grade*	Coefficient (b)	Exp(b)	% Annual Change (95% CI)
End of study cases (last 4 PSAs in 928):				
Placebo	High	0.106	1.110	11 (8–15)
Placebo	Low	0.048	1.049	5 (4–6)
Finasteride	High	0.113	1.120	12 (7–18)
Finasteride	Low	0.055	1.057	6 (3–9)
Overall placebo	—	0.057	1.058	6 (4–7)
Overall finasteride	—	0.070	1.073	7 (4–10)
Neg on end of study biopsy (8,620 noncases):				
Placebo	—	0.031	1.032	3 (2.9–4)
Finasteride	—	−0.018	0.982	−2 (−2.0–1.2)

* Gleason score at least 7 defined as high grade.

The impact of finasteride on PSA growth differed in cancer cases and subjects without cancer at the end of the study. Table 4 shows that in subjects without cancer finasteride was associated with a general decrease of approximately 5% in PSA yearly. However, in cancer cases on finasteride the estimated annual change in PSA was positive, that is 15% in interim diagnosis cases and 7% in end of study cases. Within grade prostate cancer cases on finasteride had similar growth rates compared with cases on the placebo arm of the study. Table 4 shows that interim diagnoses detected by PSA had an estimated annual increase in PSA of 20%, in contrast to nonPSA detected cases with an annual estimated change of only 1%.

DISCUSSION

To our knowledge the current study is the first to evaluate the long-term effects of finasteride on PSA in a prospectively screened, population based cohort. Previous studies have indicated that finasteride induces a substantial decrease in PSA in year 1 of treatment. Our analysis of PSA trajectories after this time indicates that PSA in normal men on finasteride continues with time to slowly diverge from that in normal men who are not being treated. The figure shows that after 1 year median PSA in placebo subjects without cancer was approximately twice that observed in treated subjects. However, after 7 years median PSA in placebo subjects without cancer was 2.5 times that observed in treated subjects. The clinical implication of this finding is that men receiving finasteride in the long term may require a PSA adjustment factor that is greater than 2 to be comparable with what is generally considered to be the normal range. This adjustment factor, which would be used as a multiplicative inflation factor on measured PSA, would increase with the duration of therapy and allow the timely detection of new prostate cancers that develop while patients are on finasteride. Based on the figure an adjustment factor that would make median PSA in men without cancer on finasteride comparable to that of normal men would increase from 2 to 2.5 during 7 years.

The long-term decrease in PSA in normal men on finasteride contrasts with the slow increase in PSA in prostate cancer cases on finasteride. Thus, in men with cancer the increase in PSA due to disease progression apparently dominates any decrease associated with the effect of finasteride on prostate epithelium. In fact, we found that PSA increases by grade in interim and end of study cases in the finasteride arm were generally comparable and in some cases greater than those observed on the control arm of the trial.

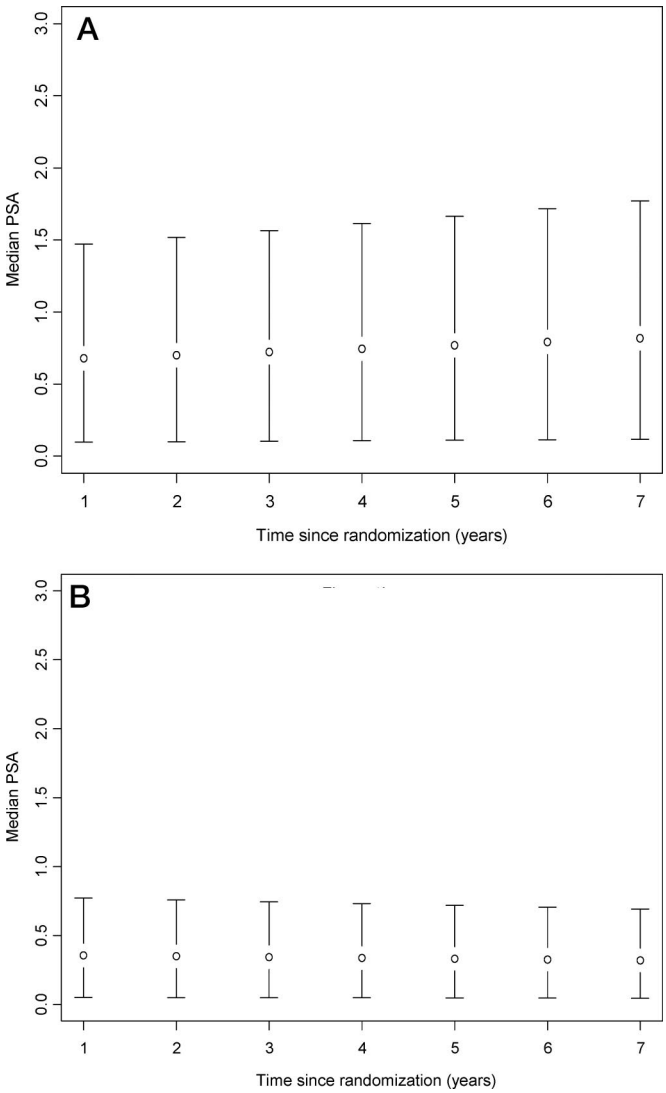
It is noteworthy but not surprising that PSA growth in PSA detected interim cases significantly surpassed that in nonPSA detected interim cases in the finasteride and placebo groups. We found this to be the case, although our analysis excluded the final PSA measurement from the data on interim cases. In interim cases detected by DRE annual PSA growth was similar to that observed in end of study cases. This finding is consistent with the existence of prostate cancers that do not emit PSA,[15] at least at early stages of progression, and it may explain in part the finding that approximately 15% of men with normal PSA who underwent biopsy at the end of the study were found to harbor prostate cancer.[16]

How do our estimated PSA growth rates compare with those in prior studies? Prior studies show an average annual PSA increase before diagnosis of 17%[17] to 33%.[18] These investigators studies retrospectively analyzed stored serum

TABLE 4. *Estimated annual percent change in PSA in interim diagnoses by detection mode*

Arm	Grade*	Coefficient (b)	Exp(b)	% Annual Change (95% CI)
Diagnosed by increased PSA at interim biopsy (435 pts):				
Placebo	High	0.159	1.172	17 (11–24)
Placebo	Low	0.089	1.093	9 (6–12)
Finasteride	High	0.211	1.235	24 (13–35)
Finasteride	Low	0.141	1.151	15 (9–22)
Overall placebo	—	0.116	1.123	12 (10–15)
Overall finasteride	—	0.184	1.202	20 (14–27)
Diagnosed by absent increased PSA at interim biopsy (236 pts):				
Placebo	High	0.081	1.084	8 (2–15)
Placebo	Low	0.058	1.060	6 (4–8)
Finasteride	High	0.027	1.027	2 (−7–13)
Finasteride	Low	0.004	1.004	0.4 (−5–6)
Overall placebo	—	0.062	1.063	6 (4–9)
Overall finasteride	—	0.010	1.010	1 (−5–7)

Last 4 PSAs, excluding final PSA.
* Gleason score at least 7 defined as high grade.



Estimated median PSA in men without prostate cancer at study end. *A*, placebo arm. *B*, finasteride arm.

samples in men later diagnosed clinically with prostate cancer. We observed considerably lower growth rates (6% to 11%) in cases on the PCPT placebo arm. There are several possible explanations for this finding. 1) It may simply reflect the fact that PCPT was a prospective screening study with an end of study biopsy and, therefore, it was designed to identify cases at an early natural history stage. This contrasts with retrospective, stored serum studies, in which analyzed cases were diagnosed clinically before the PSA era. 2) Although we focused on PSA measured within a few years prior to diagnosis, we may still have included some years in which the disease was not yet present, which would have diluted our growth rate estimates. 3) It is possible that PCPT cases, of which the majority were detected by screening or end of study biopsy, are on average biologically different from clinical cases represented in prior studies. A recent analysis of PSA growth that combined data across 3 prior studies[19] showed that cases destined to present clinically with localized disease had average annual PSA increases prior to diagnosis of approximately 15%, in contrast to cases destined to present with metastatic disease, whose average estimated annual increase was greater than 60%. This result supports the notion that PCPT detected cases with their lower PSA growth rates may include many cases of disease that would not have metastasized in the absence of PSA screening.

CONCLUSIONS

We noted that finasteride has a sustained effect on PSA in normal men but after cancer develops PSA grows equally rapidly in men on and off treatment. In addition to clarifying the long-term impact of finasteride on PSA, these findings suggest that the duration of finasteride treatment should be considered when determining whether PSA in an individual is or is not within the normal range.

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